PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
JAMES M. KANAGY
SMITHKLINE BEECHAM CORP.
CORPORATE INTELLECTURAL
PROPERTY, UW 2220
709 SWEDELAND ROAD
PO BOX 1539
KING OF PRUSSIA, PA 19406-0939

PCT

2000 OCT 23 A 10:52

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference P50972	Date of Mailing *(day/month/year)* 18 OCT 2000 **FOR FURTHER ACTION** **See paragraphs 1 and 4 below**
International application No. PCT/US00/21434	International filing date *(day/month/year)* 04 AUGUST 2000
Applicant SMITHKLINE BEECHAM CORPORATION	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PAUL J. KILLOS Dorothea Lawrence for Telephone No. (703) 308-1235

Form PCT/ISA/220 (July 1998)★

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
JAMES M. KANAGY
SMITHKLINE BEECHAM CORP.
CORPORATE INTELLECTURAL
PROPERTY, UW 2220
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[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

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Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PAUL J. KILLOS Dorothea Lawrence for Telephone No. (703) 308-1235

Form PCT/ISA/220 (July 1998)★ *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P50972	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US00/21434	International filing date *(day/month/year)* 04 AUGUST 2000	(Earliest) Priority Date *(day/month/year)* 06 AUGUST 1999
Applicant SMITHKLINE BEECHAM CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readable form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/21434

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07C. 255/00
US CL : 558/365, 404

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 558/365, 404

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN CAS FILE REGISTRY

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,552,438 A (CHRISTENSEN, IV) 03 Septembher 1996, see entire document.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 30 SEPTEMBER 2000	Date of mailing of the international search report 18 OCT 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Dorothea Lawrence for PAUL J. KILLOS Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 May 2001 (14.05.01)	
International application No. PCT/US00/21434	**Applicant's or agent's file reference** P50972
International filing date (day/month/year) 04 August 2000 (04.08.00)	**Priority date** (day/month/year) 06 August 1999 (06.08.99)
Applicant DIEDERICH, Ann, M. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

13 February 2001 (13.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Zakaria EL KHODARY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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07/968,762 30 October 1992 (30.10.92) US

(60) Parent Applications or Grants
(63) Related by Continuation
US 07/968,762 (CIP)
Filed on 30 October 1992 (30.10.92)
US 07/862,030 (CIP)
Filed on 2 April 1992 (02.04.92)

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

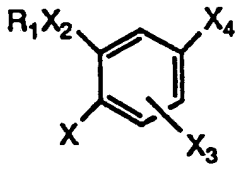
(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : CHRISTENSEN, Siegfried, B., IV [US/US]; 2216 Race Street, Philadelphia, PA 19103 (US).

(74) Agents: KANAGY, James, M. et al.; SmithKline Beecham Corporation, Corporate Patents - U.S., UW2220, 709 Swedeland Road, P.O. Box 1538, King of Prussia, PA 19406-0939 (US).

(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, RO, RU, SD, SE, SK, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.

(54) Title: COMPOUNDS USEFUL FOR TREATING ALLERGIC AND INFLAMMATORY DISEASES



(I)

(57) Abstract

Novel compounds of formula (I) are described herein. These compounds inhibit the production of Tumor Necrosis Factor and are useful in the treatment of disease states mediated or exacerbated by TNF production. The compounds of the present invention are also useful in the mediation or inhibition f enzymatic or catalytic activity of phosphodiesterase IV and are therefore useful in the treatment of disease states in need of mediation or inhibition thereof.

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BG	Bulgaria	HU	Hungary	PL	Poland
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FI	Finland	MN	Mongolia		

"Compounds Useful for Treating Allergic and Inflammatory Diseases"

Field of Invention

The present invention relates to novel compounds, pharmaceutical compositions containing these compounds, and their use in treating allergic and inflammatory diseases and for inhibiting the production of Tumor Necrosis Factor (TNF).

Background of the Invention

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli.

Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of the disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs; [Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, 17-29, 1973]. When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated, which converts Mg^{+2}-ATP to cAMP at an accelerated rate.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including: 1) airway smooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit phosphodiesterase should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cAMP breakdown in airway smooth muscle and inflammatory cells. [Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd., 1989]. Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE IV inhibitors are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case *in vivo*.

Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E_2 and prostacyclin (activators of adenylate cyclase) are elevated. Such compounds would offer a unique approach toward the pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

The compounds of this invention also inhibit the production of Tumor Necrosis Factor (TNF), a serum glycoprotein. Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis, in addition to a number of autoimmune diseases, such as multiple sclerosis, autoimmune diabetes and systemic lupus erythematosis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell-mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Viruses such as HIV-1 or HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication.

Cytokines, specifically TNF, are implicated in activated T-cell-mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by inhibition of cytokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg *et al.*, The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, 1989]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli *et al.*, Proc. Natl. Acad.

Sci., 87:782-784, 1990], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalovirus (CMV), influenza virus, adenovirus, and the herpes virus for similar reasons as those noted.

TNF is also associated with yeast and fungal infections. Specifically *Candida albicans* has been shown to induce TNF production *in vitro* in human monocytes and natural killer cells. [See Riipi *et al.*, Infection and Immunity, 58(9):2750-54, 1990; and Jafari *et al.*, Journal of Infectious Diseases, 164:389-95, 1991. See also Wasan *et al.*, Antimicrobial Agents and Chemotherapy, 35,(10):2046-48, 1991; and Luke *et al.*, Journal of Infectious Diseases, 162:211-214,1990].

The ability to control the adverse effects of TNF is furthered by the use of the compounds which inhibit TNF in mammals who are in need of such use. There remains a need for compounds which are useful in treating TNF-mediated disease states which are exacerbated or caused by the excessive and/or unregulated production of TNF.

Summary of the Invention

This invention relates to the novel compounds of the Formula (I), as shown below, useful in the mediation or inhibition of the enzymatic activity (or catalytic activity) of phosphodiesterase IV (PDE IV). The novel compounds of the Formula (I) also have Tumor Necrosis Factor (TNF) inhibitory activity.

This invention also relates to the pharmaceutical compositions comprising a compound of the Formula (I) and a pharmaceutically acceptable carrier or diluent.

The invention also relates to a method of mediation or inhibition of the enzymatic activity (or catalytic activity) of PDE IV in mammals, including humans, which comprises administering to a mammal in need thereof an effective amount of a compound of the Formula (I), as shown below.

The invention further provides a method for the treatment of allergic and inflammatory disease which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of the Formula (I).

The invention also provides a method for the treatment of asthma which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of the Formula (I).

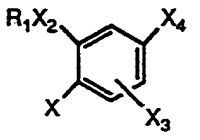
This invention also relates to a method of inhibiting TNF production in a mammal, including humans, which method comprises administering to a mammal in need of such treatment, an effective TNF inhibiting amount of a compound of the Formula (I). This method may be used for the prophylactic treatment or prevention of certain TNF mediated disease states amenable thereto.

This invention also relates to a method of treating a human afflicted with a human immunodeficiency virus (HIV), which comprises administering to such human an effective TNF inhibiting amount of a compound of the Formula (I).

The compounds of the Formula (I) are also useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*.

The compounds of the Formula (I) are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*.

The compounds of this invention are represented by Formula (I):



(I)

wherein:

R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties may be optionally substituted with one or more halogens;

m is 0 to 2;

n is 1 to 4;

r is 1 to 6;

R_4 and R_5 are independently selected from hydrogen or a C_{1-2} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3} alkyl, halo substituted aryloxyC_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group;

provided that:

a) when R_6 is hydroxyl, then m is 2; or

b) when R_6 is hydroxyl, then r is 2 to 6; or

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

X is YR_2, halogen, nitro, NR_4R_5, or formyl amine;

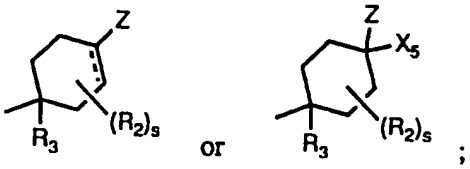
Y is O or $S(O)_{m'}$;

m' is 0, 1, or 2;

X_2 is O or NR_8;

X_3 is hydrogen or X;

X_4 is



(a) (b) ;

X_5 is H, R_9, OR_8, CN, $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8R_8$, or NR_8R_8;

R_2 is independently selected from the group consisting of $-CH_3$ and $-CH_2CH_3$ optionally substituted by 1 or more halogens;

s is 0 to 4;

R_3 is hydrogen, halogen, C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, halo-substituted C_{1-4} alkyl, $-CH=CR_{8'}R_{8'}$, cyclopropyl optionally substituted by $R_{8'}$, CN, OR_8, CH_2OR_8, NR_8R_{10}, $CH_2NR_8R_{10}$, $C(Z')H$, $C(O)OR_8$, $C(O)NR_8R_{10}$, or $C{\equiv}CR_{8'}$;

Z' is O, NR_9, NOR_8, NCN, $C(-CN)_2$, CR_8CN, CR_8NO_2, $CR_8C(O)OR_8$, $CR_8C(O)NR_8R_8$, $C(-CN)NO_2$, $C(-CN)C(O)OR_9$, or $C(-CN)C(O)NR_8R_8$;

Z is $C(Y')R_{14}$, $C(O)OR_{14}$, $C(Y')NR_{10}R_{14}$, $C(NR_{10})NR_{10}R_{14}$, CN, $C(NOR_8)R_{14}$, $C(O)NR_8NR_8C(O)R_8$, $C(O)NR_8NR_{10}R_{14}$, $C(NOR_{14})R_8$, $C(NR_8)NR_{10}R_{14}$, $C(NR_{14})NR_8R_8$, $C(NCN)NR_{10}R_{14}$, $C(NCN)SR_9$, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-, 4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-thiazolidinyl), or (2-, 4-, or 5-imidazolidinyl); wherein all of the heterocylic ring systems may be optionally substituted one or more times by R_{14};

the dotted line in formula (a) represents a single or double bond;

Y' is O or S;

R_7 is $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three fluorines, -F, -Br, -Cl, $-NO_2$, $-NR_{10}R_{11}$, $-C(O)R_8$, $-C(O)OR_8$, $-OR_8$, -CN, $-C(O)NR_{10}R_{11}$, $-OC(O)NR_{10}R_{11}$, $-OC(O)R_8$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$, $-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_9$, $-S(O)_{m'}R_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

R_{12} is C_{3-7} cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl;

R_8 is independently selected from hydrogen or R_9;

$R_{8'}$ is R_8 or fluorine;

R_9 is C_{1-4} alkyl optionally substituted by one to three fluorines;

R_{10} is OR_8 or R_{11};

R_{11} is hydrogen, or C_{1-4} alkyl optionally substituted by one to three fluorines; or when R_{10} and R_{11} are as $NR_{10}R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O/N/or S;

R_{13} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{14} is hydrogen or R7; or when R_{10} and R_{14} are as $NR_{10}R_{14}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O, N, or S;

provided that:

f) when R_{12} is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1; or

g) when X_2R_1 is OCF_2H or OCF_3, X is F, OCF_2H or OCF_3, X_3 is H, s is zero, X_5 is H, Z is $C(O)OR_{14}$ and R_{14} is C_{1-7} unsubstituted alkyl, then R3 is other than H;

or the pharmaceutically acceptable salts thereof.

Detailed Description of the Invention

This invention relates to the novel compounds of Formula (I), and to pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent. This invention also relates to a method of mediating or inhibiting the enzymatic activity (or catalytic activity) of PDE IV in a mammal in need thereof and to inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of the Formula (I).

Phosphodiesterase IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases including: asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus, [Kidney Int., 37:362, 1990; Kidney Int., 35:494, 1989] and central nervous system disorders such as depression and multi-infarct dementia.

The compounds of the Formula (I) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those that produce TNF as a result of

infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of the Formula (1). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes zoster* and *Herpes simplex*.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of the Formula (I).

The compounds of the Formula (I) may also be used in association with the veterinary treatment of animals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of the Formula (I) are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis. Additionally, the compounds of the Formula (I) may be administered in conjunction with other drugs of choice for systemic yeast and fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymixins, such as Polymycin B, the class of compounds called the imidazoles, such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itranazole, and the class of compound called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

The co-administration of the anti-fungal agent with a compound of the Formula (I) may be in any preferred composition for that compound such as is well known to those skilled in the art, for instance the various Amphotericin B formulations. Co-administration of an anti-fungal agent with a compound of the Formula (I) may mean simultaneous administration or in practice, separate administration of the agents to the mammal but in a consecutive manner. In particular, the compounds of the Formula (I) may be co-administered with a formulation of Amphotericin B, notably for systemic fungal infections. The preferred organism for treatment is the Candida organism. The compounds of the Formula (I) may be co-administered in a similar manner with anti-viral or anti-bacterial agents.

The compounds of the Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of the Formula (I) to a mammal in need of such treatment. Preferably, a compound of the Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

When R_1 for the compounds of the Formula (I) is an alkyl substituted by 1 or more halogens, the halogens are preferably fluorine and chlorine, more preferably a C_{1-4} alkyl substituted by 1 or more fluorines. The preferred halo-substituted alkyl chain length is one or two carbons, and most preferred are the moieties $-CF_3$, $-CH_2F$, $-CHF_2$, $-CF_2CHF_2$, $-CH_2CF_3$, and $-CH_2CHF_2$. Preferred R_1 substitutents for the compounds of the Formula (I) are CH_2-cyclopropyl, CH_2-C_{5-6} cycloalkyl, C_{4-6} cycloalkyl, C_{7-11} polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or C_{1-2} alkyl optionally substituted by 1 or more fluorines, $-(CH_2)_{1-3}C(O)O(CH_2)_{0-2}CH_3$, $-(CH_2)_{1-3}O(CH_2)_{0-2}CH_3$, and $-(CH_2)_{2-4}OH$.

When the R_1 term contains the moiety (CR_4R_5), the R_4 and R_5 terms are independently hydrogen or alkyl. This allows for branching of the individual methylene units as $(CR_4R_5)_n$ or $(CR_4R_5)_m$; each repeating methylene unit is independent of the other, e.g., $(CR_4R_5)_n$ wherein n is 2 can be $-CH_2CH(-CH_3)-$, for instance. The individual hydrogen atoms of the repeating methylene unit or the branching hydrocarbon can optionally be substituted by fluorine independent of each other to yield, for instance, the preferred R_1 substitutions, as noted above.

When R_1 is a C_{7-11} polycycloalkyl, examples are bicyclo[2.2.1]-heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo[5.2.1.$0^{2,6}$]decyl, etc. additional examples of which are described in Saccamano *et al.*, WO 87/06576, published 5 November 1987, whose disclosure is incorporated herein by reference in its entirety.

Z is preferably $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8R_8$, $C(NR_8)NR_8R_8$, CN, $C(NOR_8)R_8$, $C(O)NR_8NR_8C(O)R_8$, $C(NR_8)NR_8R_8$, $C(NCN)NR_8R_8$, $C(NCN)SR_9$, (1-, 4- or 5-{R_8}-2-imidazolyl), (1-, 4- or 5-{R_8}-3-pyrazolyl), (1-, 2- or 5-{R_8}-4-triazolyl[1,2,3]), (1-, 2-, 4- or 5-{R_8}-3-triazolyl[1,2,4]), (1- or 2-{R_8}-5-tetrazolyl), (4- or 5-{R_8}-2-oxazolyl), (3- or 4-{R_8}-5-isoxazolyl), (3-{R_8}-5-oxadiazolyl[1,2,4]), (5-{R_8}-3-oxadiazolyl[1,2,4]), (5-{R_8}-2-oxadiazolyl[1,3,4]), (5-{R_8}-2-thiadiazolyl[1,3,4]), (4- or 5-{R_8}-2-thiazolyl), (4- or 5-{R_8}-2-oxazolidinyl), (4- or 5-{R_8}-2-thiazolidinyl),(1-, 4- or 5-{R_8}-2-imidazolidinyl); most preferred are those compounds wherein the R_8 group of Z is R_4.

X_5 is preferably hydrogen, C_{1-2} alkyl optionally substituted by one to three fluorines, OR_8, CN, $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8R_8$, or NR_8R_8.

Preferred X groups for Formula (I) are those wherein X is YR_2 and Y is oxygen. The preferred X_2 group for Formula (I) is that wherein X_2 is oxygen. The preferred X_3 group for Formula (I) is that wherein X_3 is hydrogen. Preferred R_2 groups, where applicable, are C_{1-2} alkyl optionally substituted by 1 or more halogens. The halogen atoms are preferably fluorine and chlorine, more preferably fluorine. More preferred R_2 groups are those wherein R_2 is methyl, or the fluoro-substituted alkyls, specifically a C_{1-2} alkyl, such as a $-CF_3$, $-CHF_2$, or $-CH_2CHF_2$ moiety. Most preferred are the $-CHF_2$ and $-CH_3$ moieties.

Preferred R_3 moieties are $C(O)NH_2$, $C{\equiv}CR_8$, CN, $C(Z')H$, CH_2OH, CH_2F, CF_2H, and CF_3. More preferred are $C{\equiv}CH$ and CN. Z' is preferably O or NOR_8.

Preferred R_7 moieties include optionally substituted -$(CH_2)_{1-2}$(cyclopropyl), -$(CH_2)_{0-2}$(cyclobutyl), -$(CH_2)_{0-2}$(cyclopentyl), -$(CH_2)_{0-2}$(cyclohexyl), -$(CH_2)_{0-2}$(2-, 3- or 4-pyridyl), -$(CH_2)_{1-2}$(2-imidazolyl), -$(CH_2)_2$(4-morpholinyl), -$(CH_2)_2$(4-piperazinyl), -$(CH_2)_{1-2}$(2-thienyl), -$(CH_2)_{1-2}$(4-thiazolyl), and -$(CH_2)_{0-2}$phenyl;

Preferred rings when R_{10} and R_{11} in the moiety -$NR_{10}R_{11}$ together with the nitrogen to which they are attached form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O/N/ or S include, but are not limited to 1-imidazolyl, 2-(R_8)-1-imidazolyl, 1-pyrazolyl, 3-(R_8)-1-pyrazolyl, 1-triazolyl, 2-triazolyl, 5-(R_8)-1-triazolyl, 5-(R_8)-2-triazolyl, 5-(R_8)-1-tetrazolyl, 5-(R_8)-2-tetrazolyl, 1-tetrazolyl, 2-tetrazloyl, morpholinyl, piperazinyl, 4-(R_8)-1-piperazinyl, or pyrrolyl ring.

Preferred rings when R_{10} and R_{14} in the moiety -$NR_{10}R_{14}$ together with the nitrogen to which they are attached may form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S include, but are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazolyl, 2-triazolyl, 1-tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, and pyrrolyl. The respective rings may be additionally substituted, where applicable, on an available nitrogen or carbon by the moiety R_7 as described herein for Formula (I). Illustrations of such carbon substitutions includes, but are not limited to, 2-(R_7)-1-imidazolyl, 4-(R_7)-1-imidazolyl, 5-(R_7)-1-imidazolyl, 3-(R_7)-1-pyrazolyl, 4-(R_7)-1-pyrazolyl, 5-(R_7)-1-pyrazolyl, 4-(R_7)-2-triazolyl, 5-(R_7)-2-triazolyl, 4-(R_7)-1-triazolyl, 5-(R_7)-1-triazolyl, 5-(R_7)-1-tetrazolyl, and 5-(R_7)-2-tetrazolyl. Applicable nitrogen substitution by R_7 includes, but is not limited to, 1-(R_7)-2-tetrazolyl, 2-(R_7)-1-tetrazolyl, 4-(R_7)-1-piperazinyl. Where applicable, the ring may be substituted one or more times by R_7.

Preferred groups for $NR_{10}R_{14}$ which contain a heterocyclic ring are 5-(R_{14})-1-tetrazolyl, 2-(R_{14})-1-imidazolyl, 5-(R_{14})-2-tetrazolyl, or 4-(R_{14})-1-piperazinyl.

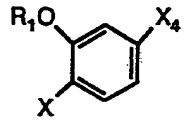
Preferred rings for R_{13} include (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-, 4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-thiazolidinyl), or (2-, 4-, or 5-imidazolidinyl).

When the R_7 group is optionally substituted by a heterocyclic ring such as imidazolyl, pyrazolyl, triazolyl, tetrazolyl, or thiazolyl, the heterocyclic ring itself may be optionally substituted by R_8 either on an available nitrogen or carbon atom, such as 1-(R_8)-2-imidazolyl, 1-(R_8)-4-imidazolyl, 1-(R_8)-5-imidazolyl, 1-(R_8)-3-pyrazolyl, 1-(R_8)-4-pyrazolyl, 1-(R_8)-5-pyrazolyl, 1-(R_8)-4-triazolyl, or 1-(R_8)-5-triazolyl. Where applicable, the ring may be substituted one or more times by R_8.

Preferred are those compounds of the Formula (I) whèrein R_1 is -CH_2-cyclopropyl, -CH_2-C_{5-6} cycloalkyl, -C_{4-6} cycloalkyl, tetrahydrofuran-3-yl, (3- or 4-cyclopentenyl), benzyl or -C_{1-2} alkyl optionally substituted by 1 or more fluorines, and -$(CH_2)_{2-4}$ OH; R_2 is methyl or fluoro-substituted alkyl, R_3 is CN or C≡CR_8; and X is YR_2.

Most preferred are those compounds wherein R_1 is -CH_2-cyclopropyl, cyclopentyl, methyl or CF_2H; R_3 is CN or C≡CH; X is YR_2; Y is oxygen; X_2 is oxygen; X_3 is hydrogen; and R_2 is CF_2H or methyl.

A preferred subgenus of the compounds of the Formula (I) is the compounds of the Formula (Ia)



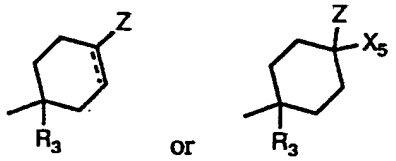
(Ia)

wherein:

R_1 is CH_2-cyclopropyl, CH_2-C_{5-6} cycloalkyl, C_{4-6} cycloalkyl, C_{7-11} polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or C_{1-2} alkyl optionally substituted by 1 or more fluorines, -$(CH_2)_{1-3}C(O)O(CH_2)_{0-2}CH_3$, -$(CH_2)_{1-3}O(CH_2)_{0-2}CH_3$, and -$(CH_2)_{2-4}OH$;

X is YR_2, halogen, nitro, NR_4R_5, or formyl amine;

X_4 is



(a) (b) ;

X_5 is H, R_9, OR_8, CN, $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8R_8$, or NR_8R_8;

Y is O or $S(O)_{m'}$;

m' is 0, 1, or 2;

R_2 is -CH_3 or -CH_2CH_3 optionally substituted by 1 or more halogens;

R_3 is hydrogen, C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, halo-substituted C_{1-4} alkyl, CN, CH_2OR_8, C(Z')H, $C(O)OR_8$, $C(O)NR_8R_{10}$, or C≡CR_8;

Z' is O or NOR_8;

Z is $C(O)R_{14}$, $C(O)OR_{14}$, $C(O)NR_{10}R_{14}$, $C(NR_{10})NR_{10}R_{14}$, CN, $C(NOR_8)R_{14}$, $C(O)NR_8NR_8C(O)R_8$, $C(O)NR_8NR_{10}R_{14}$, $C(NOR_{14})R_8$, $C(NR_8)NR_{10}R_{14}$, $C(NR_{14})NR_8R_8$, $C(NCN)NR_{10}R_{14}$, $C(NCN)SR_9$, (1-, 4- or 5-{R_{14}}-2-imidazolyl), (1-, 4- or 5-{R_{14}}-3-pyrazolyl), (1-, 2- or 5-{R_{14}}-4-triazolyl[1,2,3]), (1-, 2-, 4- or 5-{R_{14}}-3-triazolyl[1,2,4]), (1- or 2-{R_{14}}-5-tetrazolyl), (4- or 5-{R_{14}}-2-oxazolyl), (3- or 4-{R_{14}}-5-isoxazolyl), (3-{R_{14}}-5-oxadiazolyl[1,2,4]), (5-{R_{14}}-3-oxadiazolyl[1,2,4]), (5-{R_{14}}-2-oxadiazolyl[1,3,4]), (5-{R_{14}}-2-thiadiazolyl[1,3,4]), (4- or 5-{R_{14}}-2-thiazolyl),

(4- or 5-{R_{14}}-2-oxazolidinyl), (4- or 5-{R_{14}}-2-thiazolidinyl),(1-, 4- or 5-{R_{14}}-2-imidazolidinyl);

R_7 is -$(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three fluorines, -F, -Br, -Cl, -NO_2, -$NR_{10}R_{11}$, -$C(O)R_8$, -$C(O)OR_8$, -OR_8, -CN, -$C(O)NR_{10}R_{11}$, -$OC(O)NR_{10}R_{11}$, -$OC(O)R_8$, -$NR_{10}C(O)NR_{10}R_{11}$, -$NR_{10}C(O)R_{11}$, -$NR_{10}C(O)OR_9$, -$NR_{10}C(O)R_{13}$, -$C(NR_{10})NR_{10}R_{11}$, -$C(NCN)NR_{10}R_{11}$, -$C(NCN)SR_9$, -$NR_{10}C(NCN)SR_9$, -$NR_{10}C(NCN)NR_{10}R_{11}$, -$NR_{10}S(O)_2R_9$, -$S(O)_{m'}R_9$, -$NR_{10}C(O)C(O)NR_{10}R_{11}$, -$NR_{10}C(O)C(O)R_{10}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

R_{12} is C_3-C_7 cycloalkyl, (2-, 3- or 4-pyridyl), (1- or 2-imidazolyl), piperazinyl, morpholinyl, (2- or 3-thienyl), (4- or 5-thiazolyl), or phenyl;

the dotted line formula (a) represents a single or double bond;

R_8 is independently selected from hydrogen or R_9;

R_9 is C_{1-4} alkyl optionally substituted by one to three fluorines;

R_{10} is OR_8 or R_{11};

R_{11} is hydrogen or C_{1-4} alkyl optionally substituted by one to three fluorines; or when R_{10} and R_{11} are as $NR_{10}R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O/N/or S;

R_{13} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{14} is hydrogen or R_7; or when R_{10} and R_{14} are as $NR_{10}R_{14}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O/N/or S;

provided that:

a) when R_{12} is N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, or N-morpholinyl, then q is not 1; or

b) when R_1 is CF_2H or CF_3, X is F, OCF_2H, or OCF_3, X_5 is H, Z is $C(O)OR_{14}$ and R_{14} is C_{1-7} unsubstituted alkyl, then R_3 is other than H;

or the pharmaceutically acceptable salts thereof.

Exemplified compounds of Formula (I) are:

methyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylate;

4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylic acid;

methyl *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl *trans*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl *cis*- [4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate];

methyl *trans*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate], *tris*(hydroxymethyl)ammonium methane salt;

cis-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylate];

methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-cyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamide];

cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carboxamide];

trans-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carboxamide];

cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carbohydrazide];

cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-(2-acetylcarbohydrazide)];

cis-{4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(3-methyl[1,2,4]oxadiazol-5-yl)cyclohexane};

cis-{4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]oxadiazol-5-yl)cyclohexane};

cis-{4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]thiadiazol-5-yl)cyclohexane};

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-1-tris(methylthio)methylcyclohexane];

methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxamide];

methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxy-cyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1-carboxaldehyde];

methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylate];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid];

methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylate];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamic acid];

N-methyl-*cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamic acid];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-N-(2-cyanoethyl)carboxamide];

cis-[1-(2-cyanoethyl)-5-{4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl}tetrazole]; and

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-(tetrazol-5-yl)cyclohexane].

Some compounds of Formula (I) may exist in both racemic and optically active forms; some may also exist in distinct diastereomeric forms possessing distinct physical and

biological properties. All of these compounds are considered to be within the scope of the present invention. Therefore another aspect of the present invention is the administration of either a racemate, a single enanti meric form, a single diastereomeric form, or mixtures thereof.

The terms *cis* and *trans* denote stereochemistry at the C-1 position of the cyclohexane ring relative to the R3 group at the C-4 position.

The terms"C_{1-3} alkyl", "C_{1-4} alkyl", "C_{1-6} alkyl" or "alkyl" include both straight or branched chain radicals of 1 to 10, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, *tert*-butyl, and the like. "Alkenyl" includes both straight or branched chain radicals of 1 to 6 carbon lengths, unless the chain length is limited thereto, including but not limited to vinyl, 1-propenyl, 2-propenyl, 2-propynyl, or 3-methyl-2-propenyl. "Cycloalkyl" or "cycloalkyl alkyl" includes groups of 3-7 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl, or cyclohexyl. "Aryl" or "aralkyl", unless specified otherwise, means an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl, or naphthyl. Preferably the aryl is monocyclic, i.e, phenyl. The alkyl chain includes both straight or branched chain radicals of 1 to 4 carbon atoms. "Heteroaryl" as used herein, is meant an aromatic ring system containing one or more heteroatoms, such as imidazolyl, triazolyl, oxazolyl, pyridyl, pyrimidyl, pyrazolyl, pyrrolyl, furanyl, or thienyl. "Halo" as used herein is meant all halogens, i.e., chloro, fluoro, bromo, or iodo.

The phrase "inhibiting the production of IL-1" or "inhibiting the production of TNF" means:

a) a decrease of excessive *in vivo* IL-1 or TNF levels, respectively, in a human to normal levels or below normal levels by inhibition of the *in vivo* release of IL-1 by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the translational or transcriptional level, of excessive *in vivo* IL-1 or TNF levels, respectively, in a human to normal levels or below normal levels; or

c) a down regulation, by inhibition of the direct synthesis of IL-1 or TNF levels as a postranslational event.

"TNF mediated disease or disease states" means any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF-ß (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-α and TNF-ß are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise. Preferably TNF-α is inhibited.

"Cytokine" means any secreted polypeptide that affects the functions of cells, and is a molecule which modulates interactions between cells in immune, inflammatory, or hematopoietic responses. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte, but many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes, and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines for the present invention include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF-α) and Tumor Necrosis Factor-beta (TNF-ß).

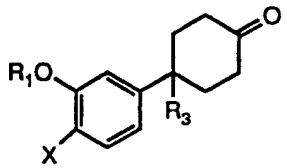
The cytokine inhibited by the present invention for use in the treatment of a HIV-infected human must be a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication, and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration. Preferrably this cytokine is TNF-α.

All of the compounds of Formula (I) are useful in the method of inhibiting the production of TNF, preferably by macrophages, monocytes or macrophages and monocytes, in a mammal, including humans, in need thereof. All of the compounds of Formula (I) are useful in the method of inhibiting or mediating the enzymatic or catalytic activity of PDE IV and in treatment of disease states mediated thereby.

METHODS OF PREPARATION:

Preparing compounds of the Formula (I) can be carried out by one of skill in the art according to the procedures outlined in the Examples, *infra*. The preparation of any remaining compounds of the Formula (I) not described therein may be prepared by the analogous processes disclosed herein which comprise:

a) for compounds of the Formula (I) wherein R_3 is H, CN, OR_9, C_{1-4} alkyl or C_{1-4} halosubstituted alkyl, wherein X or X_3 is other than Br, I, NO_2, amino, formyl amine or S(O)m' when m' is 1 or 2, wherein Z is CHO and the double bond is present, reacting a compound of the Formula (2)



(2)

wherein R_1 represents R_1 as defined in relation to Formula (I) or a group convertable to R_1 and X and X_3 represent X and X_3 as defined in relation to Formula (I) or a group convertable to X or X_3 and R_3 represents R_3 as defined in relation to Formula (I) or a group convertable to R_3, with nitromethane in a suitable non-reacting solvent in the presence of a base (catalyst)

to provide compounds of the Formula (I) wherein R_3 is H, CN, OR_9, C_{1-4} alkyl or C_{1-4} halosubstituted alkyl, wherein X and X_3 are other than Br, I, NO_2, amino, formyl amine or S(O)m' when m' is 1 or 2, wherein Z is CH_2NO_2 and the double bond is present; treatment of such compounds with a base, such as sodium methoxide, in the presence of, e.g., buffered titanium trichloride, provides compounds of the Formula (I) wherein R_3 is H, CN, OR_9, C_{1-4} alkyl or C_{1-4} halosubstituted alkyl, wherein X or X_3 are other than Br, I, NO_2, amino, formyl amine or S(O)m' when m' is 1 or 2 and wherein Z is CHO and the double bond is present. Double bond reduction of such compounds of the Formula (I) provides the corresponding saturated ring Formula (I) compounds; oxidation of the aldehyde function of either these saturated or unsaturated compounds of the Formula (I) provides the corresponding Formula (I) carboxylates (Z = COOH), which may be converted by standard procedures with proper manipulation of any chemically sensitive functional groups to the corresponding ester, amide, nitrile, oxazolidinone, etc., Z groups of the Formula (I).

Alternatively, reaction of a compound of the Formula (2) with, e.g., tosylmethyl isocyanide and potassium t-butoxide (followed by hydrolysis) or lithium methoxyphenylthiotrimethylsilylmethane (followed by hydrolysis) provides compounds of the Formula (I) wherein R_3 is H, CN, OR_9 , C_{1-4} alkyl or C_{1-4} halosubstituted alkyl, wherein X and X_3 are other than Br, I, NO_2, amino, formyl amine or S(O)m' when m' is 1 or 2, wherein Z is CO_2R_{15}, the double bond is present, and R_{15} is H or simple alkyl; these then may be converted by standard procedures with proper manipulation (protection/deprotection) of any chemically sensitive functional groups to the corresponding ester, amide, nitrile, oxazolidinone, etc., Z groups of the Formula (I).

Alternatively, reaction of a compound of the Formula (2) with, e.g., triflic anhydride in the presence of an appropriate tertiary amine base, or with an alkyl lithium at a reduced temperature followed by treatment with N-phenyl trifluorosulfonimide, provides the corresponding enol triflate, which is then reacted with carbon monoxide in the presence of an alcohol or amine and an appropriate palladium catalyst to provide compounds of the Formula (I) wherein R_3 is H, CN, OR_9 , C_{1-4} alkyl or C_{1-4} halosubstituted alkyl, wherein X and X_3 are other than Br, I, NO_2, amino, formyl amine or S(O)m' when m' is 1 or 2, wherein Z is CO_2R_{15} or $CONR_{10}R_{14}$, the double bond is present, and R_{15} is H or simple alkyl; these then may be converted by standard procedures with proper manipulation (protection/deprotection) of any chemically sensitive functional groups to the corresponding ester, amide, nitrile, oxazolidinone, etc., Z groups of the Formula (I).

Alternatively, reaction of a compound of the Formula (2) with, e.g., lithium tris(methylthio)methane at reduced temperature, followed by mercury salt hydrolysis and alcohol treatment provides compounds of the Formula (I) wherein R_3 is H, CN, OR_9 , C_{1-4} alkyl or C_{1-4} halosubstituted alkyl, wherein X and X_3 are other than Br, I, NO_2, amino, formyl amine or S(O)m' when m' is 1 or 2, wherein Z is CO_2R_{15} and X_5 is OH, the double bond is absent, and R_{15} is H or simple alkyl. Such compounds may also be obtained by

reaction of a compound of the Formula (2) with trimethylsulfoxonium iodide or trimethylsulfonium iodide and an appropriate base, such as sodium hydride, to provide the *exo*-epoxide followed by treatment with aqueous potassium hydroxide in, e.g., dimethylsulfoxide and oxidation of the resulting primary alcohol to the carboxyl provides compounds of the Formula (I) wherein R_3 is H, CN, OR9 , C_{1-4} alkyl or C_{1-4} halosubstituted alkyl, wherein X and X_3 are other than Br, I, NO_2, amino, formyl amine or S(O)m' when m' is 1 or 2, wherein Z is CO_2R_{15} and X_5 is OH, the double bond is absent, and R_{15} is H or simple alkyl; the R_5 hydroxyl may be alkylated and these compounds then may be converted by standard procedures with proper manipulation (protection/deprotection) of any chemically sensitive functional groups to the corresponding ester, amide, nitrile, oxazolidinone, etc., Z groups of the Formula (I).

Alternatively, reaction of a compound of the Formula (2) with, e.g., 2-lithio-2-(trimethylsilyl)-1,3-dithiane followed by acidic hydrolysis with a mercury salt, such as mercury (II) chloride, or reaction of a compound of the Formula (2) with, e.g., sodio-[diethyl *t*-butoxy(cyano)methyl phosphonate] followed by treatment with acetic anhydride and a zinc halide and then followed by treatment with an alkoxide provides compounds of the Formula (I) wherein R_3 is H, CN, OR9 , C_{1-4} alkyl or C_{1-4} halosubstituted alkyl, wherein X and X_3 are other than Br, I, NO_2, amino, formyl amine or S(O)m' when m' is 1 or 2, wherein Z is CO_2R_{15}, the double bond is not present, and R_{15} is H or simple alkyl and R_5 is H; these then may be converted by standard procedures with proper manipulation (protection/deprotection) of any chemically sensitive functional groups to the corresponding ester, amide, nitrile, oxazolidinone, etc., Z groups of the Formula (I).

Preparation of such compounds of the Formula (I) wherein R_3 is C(=Z')H proceed in an analogous fashion from the compound of the Formula (2) wherein =Z' is an aldehyde protecting group, such as a dimethylacetal or a dioxolane, followed by aldehyde deprotection and subsequent manipulation by standard procedures known to those of skill in the art to the remaining compounds of the Formula (I) wherein Z' is other than O or R_3 is other than H, CN, OR9 , C_{1-4} alkyl or C_{1-4} halosubstituted alkyl.

With proper manipulation (protection/deprotection) of any chemically sensitive functional groups:

a) Compounds of the Formula (I) wherein X or X_3 are formyl amine may be formed at the last step, by formylating a compound wherein X or X_3 is NH_2, obtained by removal of a protecting group from the amine functionality; such protective groups are well known to those skilled in the art, See Greene, T. and Wuts, P.G.M., Protecting Groups in Organic Synthesis, 2nd Ed., John Wiley and Sons, New York (1991).

c) Compounds of the Formula (I) wherein X or X_3 are Br or I may be prepared from a similarly deprotected amine by diazotization of the amine and diazonium displacement.

d) Compounds of the Formula (I) wherein X or X_3 are NO_2 may be prepared from a similarly deprotected amine by oxidation of the amine to the nitro group.

e) Compounds of the Formula (I) wherein Y is S(O)m' when m' is 1 or 2 may be prepared from the compounds of the Formula (I) wherein Y is S by oxidation of the SR_2 moiety under conditions well known those skilled in the art

Compounds of the Formula (2) may be prepared in turn by the processes described in co-pending application U.S. Serial Number 07/862,083 filed 2 April 1992 and the corresponding continuation-in-part application filed on even date herewith.

It will be recognized that compounds of the Formula (I) may exist in two distinct diastereomeric forms possessing distinct physical and biological properties; such isomers may be separated by standard chromatographic methods.

The following examples and methods are provided to illustrate how the make and use the invention. These materials are not intended to limit the invention in any manner; please refer to the claims appended hereto for determining what has been reserved to the inventors hereunder.

SYNTHETIC EXAMPLES

EXAMPLE 1

Methyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylate

4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclohexenyl trifluoromethylsulfonate To a solution of diisopropylamine [1.95 milliliters (hereinafter mL), 13.9 millimoles (hereinafter mmol)] in tetrahydrofuran (12 mL) at 0° C under an argon atmosphere was added n-butyllithium (5.8 mL of 2.5M solution, 14.15 mmol), the resulting solution was stirred for 25 minutes (hereinafter min) and then was cooled to -78°C. To this was added a solution of 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one [2 grams (hereinafter g), 6.64 mmol] in tetrahydrofuran (9 mL). The resulting mixture was stirred at -78° C for 2 hours (hereinafter h), at which time N-phenyl-trifluoromethylsulfonimide (4.98 g, 13.9 mmol) was added. The mixture was allowed to warm slowly to room temperature and after 5h, the mixture was poured into water and extracted with methylene chloride. The organic extract was dried (potassium carbonate) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 4:1 hexanes/ethyl acetate, to afford an oil (1.09 g, 37%).

Methyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylate To a solution of 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclohexenyl trifluoromethylsulfonate (1.0 g, 2.24 mmol) in 1:1 methanol/N,N-dimethylformamide (8 mL) were added triethylamine (0.66 mL, 4.72 mmol) and tetrakis(triphenylphosphine)palladium (0.13 g, 0.11 mmol). The resulting mixture was stirred at room temperature in the dark under a carbon monoxide atmosphere for 3h. The mixture was partitioned between water and ethyl acetate, the organic extract was washed three times with water, once with brine, was dried (potassium carbonate) and was evaporated.

Purification by flash chromatography, eluting with 3:1 hexanes/ethyl acetate, provided an off-white solid (0.64 g, 80%): m.p. 128-129° C.
Analysis Calc. for $C_{21}H_{25}NO_4 \cdot 1/8\ H_2O$: C 70.52, H 7.12, N 3.92; found: C 70.45, H 6.93, N 3.87.

EXAMPLE 2

4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylic acid

To a solution of methyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylate (0.07 g, 0.18 mmol) in methanol (0.5 mL, containing just enough tetrahydrofuran to solubilize the ester) under an argon atmosphere was added a solution of potassium hydroxide (0.03 g, 0.55 mmol) in water (0.4 mL). The resulting mixture was stirred at room temperature for 4h, then poured into water and extracted with ethyl acetate. The aqueous phase was acidified with 3N hydrochloric acid and extracted twice with ethyl acetate. The organic phase from the acid extraction was dried (sodium sulfate) and concentrated under reduced pressure to provide a viscous oil, which solidified upon standing. The solid was recrystallized from hexanes/methylene chloride (0.05 g, 82%): m.p. 161-163°C.
Analysis Calc. for $C_{20}H_{23}NO_4 \cdot 1/2H_2O$: C 68.55, H 6.90, N 4.00; found: C 68.65, H 6.55, N 3.82.

EXAMPLE 3

Methyl *cis*- and *trans*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate]

Procedure 3A:

To a solution of methyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylate (0.26 g, 0.73 mmol) in methanol (12 mL) was added 10% palladium on activated carbon (0.15 g) and the resulting mixture was hydrogenated at 50 psi for 5h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was partitioned between methylene chloride and water, the extract was dried (potassium carbonate) and evaporated to a solid which was primarily the *cis*-ester (0.14 g, 54%): m.p. 94-95°C.
Analysis Calc. for $C_{21}H_{27}NO_4 \cdot 1/8\ H_2O$: C 70.32, H 7.38, N 3.90; found: C 70.33, H 7.59, N 3.81.

Procedure 3B:

2-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexylidene]-1,3-dithiane To a solution of 2-trimethylsilyl-1,3-dithiane (9.25 mL, 48.7 mmol) in dry tetrahydrofuran (80 mL) at 0° C under an argon atmosphere was added rapidly *n*-butyllithium (2.5M in hexanes, 19.2 mL, 48 mmol). After 10 min, the mixture was cooled to -78°C and a solution of 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one (7.53 g, 23 mmol) in

tetrahydrofuran (40 mL) was added. After 10 min, aqueous sodium chloride was added, the mixture was allowed to warm to room temperature and was diluted with water. This mixture was combined with the product of three substantially similar reactions conducted on ketone (3.04, 6.01 and 6.1 g, 48.3 mmol total), the combined mixture was extracted three times with methylene chloride, the extract was dried (magnesium sulfate) and evaporated. Purification by flash chromatography, eluting with 10% ethyl acetate/hexanes, provided a white solid (26 g, 87%): m.p. 115-116°C.

Methyl *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate] Perchloric acid (70%, 13.8 mL, 160 mmol) and mercuric chloride (34.1 g, 126 mmol) were added to a solution of 2-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexylidene]-1,3-dithiane (13 g, 31.3 mmol) in methanol (0.5 L) under an argon atmosphere and the mixture was heated at reflux for 2h and then was allowed to stir at room temperature for 42h. The mixture was diluted with methylene chloride, was filtered through Celite and the filtrate was combined with that of a similar reaction conducted concurrently on the same scale. The mixture was neutralized with aqueous sodium bicarbonate, was extracted three times with methylene chloride, the organic extract was washed three times with aqueous sodium sulfite, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 15% ethyl acetate/hexanes, provided the *cis*-ester as a white solid (12.4 g, 56%): m.p. 119-120°C, along with an additional quantity of slightly impure product (2.6 g, 12%).

Methyl *trans*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate] The *trans*-ester was also isolated from this mixture as a solid (1.04 g, 5%): m.p. 50-51° C.

Analysis Calc. for $C_{21}H_{27}NO_4 \cdot 3/4\ H_2O$: C 67.99, H 7.74, N 3.78; found: C 67.98, H 7.35, N 3.65.

EXAMPLE 4

Methyl *cis*- and *trans*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate]

Procedure 4A:

2-[4-(3,4-Bisdifluoromethoxyphenyl)-4-cyanocyclohexylidene]-2-*tert*-butyloxy acetonitrile Sodium hydride (80% dispersion, 0.35 g, 11.7 mmol) was washed three times with pentane, was suspended in tetrahydrofuran (15 mL) at room temperature under an argon atmosphere and diethyl *tert*-butyl(cyano)methylphosphonate (2.66 g, 10.7 mmol) was added. After 0.5h, a solution of 4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexan-1-one (1.77 g, 5.34 mmol) in tetrahydrofuran (5 mL) was added and the mixture was heated at reflux for 0.5h. The mixture was cooled, aqueous sodium chloride and water were added, the mixture was extracted three times with ether, the extract was dried (magnesium sulfate) and

evaporated. Purification by flash chromatography, eluting with 20% ethyl acetate/hexanes, provided the title compound as a white solid (1.18 g, 52%).

Methyl *cis*- and *trans*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate] A mixture of 2-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexylidene]-2-*tert*-butyloxy acetonitrile (0.25 g, 0.59 mmol) and zinc chloride (0.1 g, 0.7 mmol) in acetic anhydride (1.5 mL) under an argon atmosphere was heated at reflux for 10 min, was cooled, was diluted with water and was extracted three times with ether. The organic extract was washed with water, dried (magnesium sulfate) and evaporated. A solution of this acetate in methanol (6 mL) was treated with a solution of sodium methoxide (25% in methanol, 0.17 mL, 0.71 mmol) and the mixture was stirred under an argon atmosphere for 2h. The mixture was acidified with hydrochloric acid (1N), water was added and the mixture was extracted three times with methylene chloride. The organic extract was dried (magnesium sulfate) and evaporated. Purification by flash chromatography and eluting with 20% ethyl acetate/hexanes provided the *trans*-isomer as a colorless oil (0.07 g, 30%).
Analysis Calc. for $C_{17}H_{17}F_4NO_4$: C 54.40, H 4.57, N 3.73; found: C 54.57, H 4.51, N 3.58.
The *cis*-isomer was also isolated as a yellow oil (0.1 g, 47%).

Procedure 4B:

Methyl *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate] A solution of *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylic acid (EXAMPLE 10, 0.07 g, 0.19 mmol) and trimethylsilyl chloride (0.12 mL, 0.95 mmol) in methanol (5 mL) was stirred at room temperature under an argon atmosphere for 24h. The solvent was evaporated and the residue was purified by flash chromatography, eluting with 15% ethyl acetate/hexanes, provided a colorless oil (0.05 g, 63%).
Analysis Calc. for $C_{17}H_{17}F_4NO_4$: C 54.40, H 4.57, N 3.73; found: C 54.45, H 4.49, N 3.42.

EXAMPLE 5

cis-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] and *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylic acid]

To a solution of methyl *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate] (0.12 g, 0.34 mmol) in methanol (0.9 mL, containing just enough tetrahydrofuran to solubilize the ester) under an argon atmosphere was added a solution of potassium hydroxide (0.06 g, 0.9 mmol) in water (0.7 mL). The resulting mixture was stirred at room temperature for 1.5h, then poured into water and extracted with ethyl acetate. The aqueous phase was acidified with 10% hydrochloric acid and extracted twice with ethyl acetate. The organic phase from the acid extraction was dried (sodium sulfate) and concentrated under reduced pressure to provide a solid. The solid was purified by flash chromatography, eluting with 4% methanol/chloroform, to provide a white solid (0.05 g, 44%): m.p. 157°C.

Analysis Calc. for $C_{20}H_{25}NO_4 \cdot 1/8H_2O$: C 68.75, H 7.40, N 4.01; found: C 68.74, H 7.08, N 3.84.

In a similar manner there was prepared:

cis-[4-(3,4-Bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylic acid] as a solid: m.p. 143-144°C.

Analysis Calc. for $C_{16}H_{15}F_4NO_4$: C 53.19, H 4.18, N 3.88; found: C 53.57, H 3.91, N 3.59.

EXAMPLE 6

cis-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate], *tris*(hydroxymethyl)ammonium methane salt

To a solution of *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] (0.17 g, 0.5 mmol) in methanol (2 mL) was added an aqueous solution of tris(hydroxymethyl)aminomethane (1.0M, 0.5 mL). After 10 min, the solvent was evaporated, toluene and methanol were added and the liquids were removed *in vacuo*. Trituration with ether provided a white solid (0.18 g, 79%): m.p. 191-194°C.

Analysis Calc. for $C_{24}H_{36}N_2O_7 \cdot 2.5H_2O$: C 56.57, H 8.11, N 5.50; found: C 56.44, H 7.75, N 5.62.

EXAMPLE 7

trans-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]

To a solution of methyl *trans*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate] (0.68 g, 1.9 mmol) in methanol (8 mL, containing just enough tetrahydrofuran to solubilize the ester) under an argon atmosphere was added water (4 mL) and potassium hydroxide (0.32 g, 5.7 mmol). The resulting mixture was stirred at room temperature for 24h, was acidified with 10% hydrochloric acid and was extracted three times with 10% methanol/methylene chloride. The organic extract was dried (magnesium sulfate) and concentrated under reduced pressure. Purification by flash chromatography, eluting with 4% methanol/methylene chloride, provided a white semi-solid (0.52 g, 80%), which was triturated with ether to yield a white solid (0.43 g): m.p. 157-158°C.

Analysis Calc. for $C_{20}H_{25}NO_4$: C 69.95, H 7.34, N 4.08; found: C 69.69, H 7.30, N 4.07.

EXAMPLE 8

cis- and *trans*-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]

8A. 2-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexylidine]-2-*tert*-butyloxy acetonitrile This compound, prepared substantially as described above for 2-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclo-hexylidene]-2-*tert*-butyloxy acetonitrile in Procedure A of EXAMPLE 4, was isolated as a white solid: m.p. 109-110°C.

8B. Methyl *cis*- and *trans*-[4-cyano-4-(3-hydroxy-4-methoxyphenyl)cyclohexane-1-carboxylate] These compounds, prepared substantially as described above for methyl *cis*- and *trans*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate] in Procedure A of EXAMPLE 4, were isolated as solids [*cis*-isomer (0.35 g, 33%): m.p. 105-106°C; *trans*-isomer (0.52g, 49%): m.p. 103-104°C].

8C. Methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxyate] A suspension of methyl *cis*-[4-cyano-4-(3-hydroxy-4-methoxyphenyl)cyclohexane-1-carboxylate] (0.35 g, 1.20 mmol), powdered potassium carbonate (0.5 g, 3.6 mmol) and bromomethyl cyclopropane (0.35 mL, 3.6 mmol) in dry dimethylformamide (15 mL) under an argon atmosphere was heated at 85°C for 4h. The mixture was cooled, was diluted with water and was extracted three times with ether. The organic extract was washed four times with water, once with brine, was dried (potassium carbonate) and was evaporated. Purification by flash chromatography, eluting with 20% ethyl acetate/hexanes, provided an oil (0.34 g, 82%).

8D. *cis*-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] The title compound, prepared substantially as described above for *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] in EXAMPLE 7, was isolated as a solid: m.p. 165-167°C .

Analysis Calc. for $C_{19}H_{23}NO_4 \cdot 1/5\ H_2O$: C 68.53, H 7.08, N 4.21; found: C 68.70, H 7.07, N 4.16.

8E. Methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxyate] The title compound, prepared substantially as described above for methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxyate] in EXAMPLE 8C was isolated as a solid: m.p. 127.5-128°C .

Analysis Calc. for $C_{20}H_{25}NO_4 \cdot 3/8\ H_2O$: C 68.60, H 7.41, N 4.00; found: C 68.50, H 7.28, N 3.88.

8F. *trans*-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] The title compound, prepared substantially as described above for *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] in EXAMPLE 7, was isolated as a solid: m.p. 148°C .

Analysis Calc. for $C_{19}H_{23}NO_4$: C 69.28, H 7.04, N 4.25; found: C 68.97, H 7.03, N 4.25.

EXAMPLE 9

cis- and *trans*-[4-Cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid]

9A. 2-[4-Cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexylidene]-1,3-dithiane This compound, prepared substantially as described above for 2-[4-cyano-4-(3-cyclopentyloxy-4-

methoxyphenyl)cyclohexylidene]-1,3-dithiane in Procedure B of EXAMPLE 3, was isolated as a solid: m.p. 84-85°C.

9B. Methyl *cis*- and *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylate] These compounds, prepared substantially as described above for methyl *cis*- and *trans*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate] in Procedure B of EXAMPLE 3, were isolated as oils.

9C. *cis*-[4-Cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid] This compound, prepared substantially as described above for *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] in EXAMPLE 7, was isolated as a solid: m.p. 134-135°C.

Analysis Calc. for $C_{19}H_{21}F_2NO_4$: C 62.46, H 5.79, N 3.83; found: C 62.15, H 5.83, N 3.88.

9D. *trans*-[4-Cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-cyclohexane-1-carboxylic acid] The title compound, prepared substantially as described above for *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] in EXAMPLE 7, was isolated as a solid: m.p. 128-129°C.

EXAMPLE 10

cis-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamide]

To a solution of methyl *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate] (0.22 g, 0.62 mmol) and formamide (0.08 mL, 2.08 mmol) at 100°C in dimethylformamide (2 mL) under an argon atmosphere was added portionwise over 20 min sodium methoxide (25% solution in methanol, 0.1 mL, 0.43 mmol). After an additional 1.25h at 100°C, the mixture was cooled, was poured into isopropanol, was filtered and the filtrate evaporated. The residue was dissolved in ethyl acetate, the organic phase was washed three times with water, was dried (magnesium sulfate) and was concentrated under reduced pressure. Purification by flash chromatography, eluting with 3% methanol/methylene chloride, provided a white foam (0.06 g, 28%).

Analysis Calc. for $C_{20}H_{26}N_2O_3 \cdot 3/8H_2O$: C 68.79, H 7.72, N 8.02; found: C 68.86, H 7.49, N 7.93.

EXAMPLE 11

cis-[4-(3,4-Bisdifluoromethoxyphenyl)-4-cyano-1-(3-methyl[1,2,4]oxadiazol-5-yl)cyclohexane]

cis-and *trans*-[4-(3,4-Bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxamide] These compounds, prepared substantially as described above for *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamide] in EXAMPLE 14, were isolated as a solid (*cis* isomer: m.p. 109-110°C) and as an oil (*trans* isomer).

cis-[4-(3,4-Bisdifluoromethoxyphenyl)-4-cyano-1-(3-methyl[1,2,4]oxadiazol-5-yl)cyclohexane] A solution of *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxamide] (0.06 g, 0.17 mmol) in N,N-dimethylacetamide dimethyl acetal (0.5 mL) was heated at 110°C under an argon atmosphere for 1h, was cooled and the solvent was evaporated. Dioxane (0.35 mL), acetic acid (0.35 mL), hydroxylamine hydrochloride (0.02 g, 0.29 mmol) and 10% aqueous sodium hydroxide (0.09 mL, 0.26 mmol) were added and the mixture was heated at 95°C under an argon atmosphere for 2.5h. The mixture was cooled, water was added, the mixture was extracted three times with methylene chloride, the organic extract was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 4% methanol/methylene chloride, provided a solid (0.03 g, 37%). This product was combined with that (0.04 g) from a similar reaction sequence and was triturated with hexane to yield a tan solid: m.p. 83-84°C.

Analysis Calc. for $C_{18}H_{17}F_4N_3O_3$: C 54.14, H 4.29, N 10.52; found: C 54.11, H 4.35, N 10.13.

EXAMPLE 12

cis-[4-(3,4-Bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]oxadiazol-5-yl)cyclohexane]

cis-[4-(3,4-Bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carbohydrazide] A solution of methyl *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate] (0.2 g, 0.53 mmol) and hydrazine hydrate (0.28 mL, 9.0 mmol) in ethanol (2.5 mL) was heated at reflux for 6h and then stirred at room temperature for 16h. Water was added, the mixture was extracted three times with methylene chloride, the extract was dried (magnesium sulfate) and evaporated. Purification by flash chromatography, eluting with 4% methanol/methylene chloride, provided a solid (0.12 g, 58%): m.p. 80-81°C.

cis-[4-(3,4-Bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-(2-acetyl-carbohydrazide)] A solution of methyl *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carbohydrazide] (0.11 g, 0.29 mmol), triethylamine (0.09 mL, 0.65 mmol) and acetic anhydride (0.05 mL, 0.54 mmol) in ethanol (7.5 mL) was heated at reflux for 1h, was cooled and the solvent was evaporated. Water was added, the mixture was extracted three times with methylene chloride, the extract was dried (magnesium sulfate) and evaporated to provide a white solid (0.11 g, 85%): m.p. 144-145°C.

cis-[4-(3,4-Bisdifluoromethoxyphenyl)-4-cyano-1-(3-methyl[1,3,4]oxadiazol-5-yl)cyclohexane] A solution of *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-(2-acetyl-carbohydrazide)] (0.1 g, 0.24 mmol) and phosphorpus oxychloride (0.25 mL, 2.68 mmol) in toluene (3 mL) was heated at reflux under an argon atmosphere for 1.5h. The mixture was cooled, water was added, the mixture was extracted three times with 5% methanol/methylene chloride, the organic extract was dried (magnesium sulfate) and was

evaporated. Purification by flash chromatography, eluting with 1:2 hexanes/ethyl acetate, provided an oil.

Analysis Calc. for $C_{18}H_{17}F_4N_3O_3$·1.0 H_2O: C 51.80, H 4.59, N 10.07; found: C 52.00, H 4.25, N 9.76.

EXAMPLE 13

cis-[4-(3,4-Bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]thiadiazol-5-yl)cyclohexane]

A solution of *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-(2-acetyl-carbohydrazide)] (0.1 g, 0.24 mmol) and Lawesson's Reagent (0.13 g, 0.32 mmol) in toluene (3 mL) was heated at reflux under an argon atmosphere for 0.5h. The mixture was cooled, saturated aqueous sodium bicarbonate was added, the mixture was extracted three times with methylene chloride, the organic extract was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 1:1 hexanes/ethyl acetate, provided a solid: m.p. 66-67°C.

Analysis Calc. for $C_{18}H_{17}F_4N_3O_2S$: C 52.04, H 4.13, N 10.12; found: C 51.67, H 4.06, N 9.92.

EXAMPLE 14

cis-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-1-tris(methylthio)methylcyclohexane]

n-Butyllithium (1.9M in hexanes, 0.4 mL, 0.76 mmol) was added dropwise over 5 min to a solution of tris(methylthio)methane (0.11 mL, 0.83 mmol) in dry tetrahydrofuran (3 mL) at -78°C under an argon atmosphere. After 15 min, a solution of 4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane (0.2 g, 0.67 mmol) in dry tetrahydrofuran (3 mL) was added dropwise over 10 min. After 0.5h, aqueous ammonium chloride was added and the mixture was allowed to warm to room temperature. The mixture was extracted three times with methylene chloride, the organic extract was dried (magnesium sulfate) and evaporated. Purification by flash chromatography, eluting with 25% ethyl acetate/hexanes, provided a white solid (0.25 g, 84%): m.p. 123-124°C.

Analysis Calc. for $C_{22}H_{31}NO_3S_3$: C 58.24, H 6.89, N 3.09; found: C 58.57, H 6.81, N 2.92.

EXAMPLE 15

Methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylate]

Mercuric chloride (0.23 g, 0.85 mmol) and mercuric oxide (0.08 g, 0.37 mmol) were added to a solution of *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-1-tris(methylthio)methylcyclohexane] (0.1 g, 0.22 mmol) in 12:1 methanol/water (2 mL) under an argon atmosphere and the mixture was allowed to stir at room temperature for 4h.

The mixture was filtered through Celite, the filtrate was diluted with water and was extracted three times with methylene chloride, the organic extract was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 35% ethyl acetate/hexanes, provided a sticky solid (0.67 g), which was triturated with ether/hexane to provide a solid (0.47 g, 59%): m.p. 102-103°C.

Analysis Calc. for $C_{20}H_{25}NO_5 \cdot 1/2\ H_2O$: C 65.20, H 7.11, N 3.80; found: C 65.31, H 6.83, N 3.54.

EXAMPLE 16

cis-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid]

The title compound, prepared substantially as described above for *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] in EXAMPLE 5, was isolated as a solid: m.p. 168-169°C .

Analysis Calc. for $C_{19}H_{23}NO_5 \cdot 1/4\ H_2O$: C 65.22, H 6.77, N 4.00; found: C 64.94, H 6.62, N 3.80.

EXAMPLE 17

cis-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxamide]

A solution of *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxy-phenyl)-1-hydroxycyclohexane-1-carboxylic acid] (0.15 g, 0.42 mmol) and a trace of sodium cyanide in methanol (1.5 mL) contained in a pressure vessel was cooled to -78 and anhydrous ammonia (2 mL) was condensed into the tube. The tube was sealed, was allowed to come to room temperature and the reaction was stirred for 2 days. The ammonia was allowed to evaporate and the reaction was partitioned between water and methylene chloride. The organic extract was dried (magnesium sulfate) and the solvent was evaporated. Purification by flash chromatography, eluting with 3% methanol/chloroform, provided a solid (0.054 g, 38%): m.p. 144-145°C.

Analysis Calc. for $C_{19}H_{24}N_2O_4 \cdot 1/4\ H_2O$: C 65.41, H 7.08, N 8.03; found: C 65.16, H 6.96, N 7.86.

EXAMPLE 18

Methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylate]

Silver (I) oxide (0.62 g, 2.7 mmol) was added to a solution of methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylate] (0.62 g, 1.7 mmol) and iodomethane (5 mL) in acetonitrile (5 mL) under an argon atmosphere and the mixture was heated at reflux in the dark for 18h. The mixture was cooled, was filtered

through Celite and the filtrate was evaporated. Purification by flash chromatography, eluting with 20% ethyl acetate/hexanes, provided a solid (0.55 g, 86%): m.p. 75-76°C.
Analysis Calc. for $C_{21}H_{27}NO_5$: C 67.54, H 7.29, N 3.75; found: C 67.46, H 7.30, N 3.80.

EXAMPLE 19

cis-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid]

The title compound, prepared substantially as described above for *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] in EXAMPLE 5, was isolated as a solid: m.p. 110-112°C.
Analysis Calc. for $C_{20}H_{25}NO_5$: C 66.84, H 7.01, N 3.90; found: C 66.64, H 7.29, N 3.95.

EXAMPLE 20

cis-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide]

A solution of *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid] (0.13 g, 0.36 mmol) and N-methylmorpholine (0.05 mL, 0.45 mmol) in 1,2-dimethoxyethane (2.5 mL) at room temperature under an argon atmosphere was treated with isobutyl chloroformate (0.05 mL, 0.39 mmol). After 10 min, concentrated ammonium hydroxide (6 drops) was added and the mixture was stirred for an additional 0.5h. Water was added, the mixture was extracted three times with 5% methanol/methylene chloride, the organic extract was dried (magnesium sulfate) and the solvent was evaporated. Purification by flash chromatography, eluting with 3% methanol/chloroform, provided a solid (0.13 g, 100%): m.p. 165-166°C.
Analysis Calc. for $C_{20}H_{26}N_2O_4 \cdot 3/8\ H_2O$: C 65.78, H 7.35, N 7.67; found: C 65.65, H 7.23, N 7.47.

EXAMPLE 21

Methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylate]

trans-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-cyclohexane-1,1-diyl]oxirane] To a mixture of 80% sodium hydride in mineral oil (0.33 g, 11 mmol) and trimethylsulfoxonium iodide (1.69 g, 7.67 mmol) at room temperature under an argon atmosphere was added dropwise dimethylsulfoxide (12 mL) and the reaction mixture was stirred for 30 min. A solution of 4-cyano-4-(3-cyclopropylmethoxy-3-methoxyphenyl) -cyclohexanone (2.00 g, 6.68 mmol) in dimethylsulfoxide (5 mL) was added and stirring was continued for 30 min. The reaction mixture was quenched with saturated ammonium chloride, was partitioned between ethyl acetate and water, was dried (magnesium sulfate) and

the solvent was removed *in vacuo* . The residue was purified by flash chromatography, eluting with 1:3 ethyl acetate/hexanes, to provide a colorless oil (1.42 g, 68%).
Analysis Calc. for $C_{19}H_{23}NO_3 \cdot H_2O$: C 68.86, H 7.30, N 4.23; found: C 69.22, H 7.11, N 4.17. Starting material was also recovered (0.6 g, 30%).

trans-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxymethyl-1-cyclohexanol] A mixture of *trans*-4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-cyclohexane-1-methyleneoxide (1.31 g, 4.18 mmol) and potassium hydroxide (0.14 g, 2.5 mmol) in 85:15 dimethylsulfoxide/water (140 mL) under an argon atmosphere was heated at 100-110°C for 1h, was cooled, was diluted with water and was extracted three times with ethyl acetate. The organic extract was washed five times with water, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 3.5:96.5 methanol/dichloromethane, provided the *trans*-isomer as a sticky white solid: m.p. 38-42°C (0.96 g, 69%).
Analysis Calc. for $C_{19}H_{25}NO_4$: C 68.86, H 7.60, N 4.23; found: C 68.96, H 7.62, N 4.03.

trans-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1-carboxaldehyde] To a solution of oxalyl chloride (0.28 mL, 3.21 mmol) in dichloromethane (3.5 mL) at -78°C under an argon atmosphere was added dropwise a solution of dimethylsulfoxide (0.46 mL, 6.48 mmol) in dichloromethane (3.5 mL) such that the internal temperature did not exceed -60°C. A solution of *trans*-4-cyano-4-(3-cyclopropylmethoxy-3-methoxyphenyl)-1-hydroxymethyl-1-cyclohexanol (0.89 g, 2.68 mmol) in dichloromethane (7 mL) was added dropwise and stirring was continued for 30 min. Triethylamine (1.80 mL, 12.9 mmol) was added over 10 min, then 5 min later, the reaction mixture was allowed to warm to room temperature over 1h. The reaction mixture was quenched with water and was extracted with three portions of dichloromethane. The combined organic layers were washed with 1% hydrochloric acid, 5% sodium carbonate and water, dried (magnesium sulfate) and the solvent was removed *in vacuo* to provide crude aldehyde (0.85 g, 97 %).

Methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1-carboxylate] To a solution of trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxaldehyde (0.79 g, 2.4 mmol) in methanol (25 mL) at 0°C under an argon atmosphere was rapidly added a solution of potassium hydroxide (0.36 g, 6.43 mmol) in methanol (5 mL), followed by a solution of iodine (0.80 g, 3.15 mmol) in methanol (5 mL). After 15 min the reaction was acidified with 1N hydrochloric acid and extracted with three portions of dichloromethane. The combined organic layers were washed with aqueous sodium bisulfite until color was discharged, then with water, dried (magnesium sulfate), and the solvent was removed *in vacuo*.. Purification by flash chromatography, eluted with 35:65 ethyl acetate/hexanes , provided a white solid (0.82 g, 94 %): m.p.148-149°C.

Analysis Calc. for $C_{20}H_{25}NO_5 \cdot 1/4\ H_2O$: C 66.01, H 7.06, N 3.84; found: C 65.86, H 6.92, N 3.85.

EXAMPLE 22

trans-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid]

The title compound, prepared substantially as described above for *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] in EXAMPLE 5, was isolated as a solid: m.p. 147-148°C.

Analysis Calc. for $C_{19}H_{23}NO_5$: C 66.07, H 6.71, N 4.06; found: C 66.02, H 6.71, N 4.04.

EXAMPLE 23

Methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylate]

The title compound, prepared substantially as described above for methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylate] in EXAMPLE 18, was isolated as a solid: m.p. 84-85°C.

Analysis Calc. for $C_{21}H_{27}NO_5$: C 67.54, H 7.29, N 3.75; found: C 67.34, H 7.25, N 3.77.

EXAMPLE 24

trans-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid]

The title compound, prepared substantially as described above for *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] in EXAMPLE 5, was isolated as a solid: m.p. 158-159°C.

Analysis Calc. for $C_{20}H_{25}NO_5 \cdot 1/4\ H_2O$: C 66.01, H 7.06, N 3.85; found: C 65.98, H 6.91, N 3.75.

EXAMPLE 25

trans-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide]

The title compound, prepared substantially as described above for *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide] in EXAMPLE 20, was isolated as a solid: m.p. 168-169°C.

Analysis Calc. for $C_{20}H_{26}N_2O_4 \cdot 1/8\ H_2O$: C 66.60, H 7.34, N 7.70; found: C 66.60, H 7.30, N 7.74.

EXAMPLE 26

cis-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamic acid]

The title compound, prepared substantially as described above for *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide] in EXAMPLE 20 but using hydroxylamine instead of ammonia, was isolated as a solid: m.p. 100-102°C. Analysis Calc. for $C_{20}H_{26}N_2O_4$: C 67.02, H 7.31, N 7.82; found: C 66.75, H 7.58, N 7.42.

EXAMPLE 27

N-Methyl-*cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamic acid]

The title compound, prepared substantially as described above for *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide] in EXAMPLE 20 but using N-methylhydroxylamine instead of ammonia, was isolated as a solid: m.p. 75-76°C.

Analysis Calc. for $C_{21}H_{28}N_2O_4 \cdot 1/4\ H_2O$: C 66.91, H 7.62, N 7.43; found: C 66.95, H 7.54, N 7.35.

EXAMPLE 28

cis-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-N-(2-cyanoethyl)carboxamide]

To a solution of *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] (0.55 g, 1.6 mmol), 1-hydroxybenzotriazole (0.24 g, 1.76 mmol) and 3-aminopropionitrile (0.11 g, 1.6 mmol) in dichloromethane (10 mL) at 0°C under an argon atmosphere was added 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.34 g, 1.76 mmol) and the mixture was allowed to warm to room temperature. After 6h, the mixture was diluted with dichloromethane, was washed twice with 10% aqueous potassium carbonate, twice with 10 % hydrochloric acid and was dried (magnesium sulfate). The solvent was evaporated and the residue was crystallized from hexanes/ethyl acetate to provide a solid (0.54 g, 85%): m.p. 146-147°C.

Analysis Calc. for $C_{23}H_{29}N_3O_3$: C 69.85, H 7.39, N 10.62; found: C 69.49 H 7.41, N 10.46.

EXAMPLE 29

cis-[1-(2-Cyanoethyl)-5-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl]tetrazole]

To a solution of *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-N-(2-cyanoethyl)carboxamide] (0.15 g, 0.37 mmol), triphenylphosphine (0.19 g, 0.73 mmol) and trimethylsilylazide (0.097 mL, 0.73 mmol) in dry tetrahydrofuran (2 mL) at room temperature under an argon atmosphere was added dropwise diethyl azodicarboxylate (0.12 mL, 0.73 mmol) and the mixture was stirred in the dark for 24h. Ceric ammonium nitrate

(0.81 g, 1.48 mmol) in water (10 mL) was added at 0°C, the mixture was extracted three times with dichloromethane, the extract was dried (magnesium sulfate) and the solvent was evaporated. Purification by flash chromatography, eluting with 2:1 ethyl acetate/hexanes, followed by recrystallization from hexanes/ethyl acetate, provided a white solid (0.03 g, 19%): m.p. 149-150°C.

Analysis Calc. for $C_{23}H_{28}N_6O_2$: C 65.69, H 6.71, N 19.99; found: C 65.45 H 6.72, N 19.91.

EXAMPLE 30

cis-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-tetrazolyl)cyclohexane]

A mixture of *cis*-[1-(2-cyanoethyl)-5-{4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl}tetrazole] (0.098 g, 0.23 mmol) and sodium hydroxide (0.018 g, 0.46 mmol) in 10:1 tetrahydrofuran/water (5 mL) at room temperature under an argon atmosphere was stirred overnight. The mixture was acidified with 3N hydrochloric acid, was extracted three times with ethyl acetate, the extract was dried (magnesium sulfate) and the solvent was evaporated. Purification by flash chromatography, eluting with 80:20:2 chloroform/methanol/water, followed by trituration with hexanes/ethyl acetate, provided a white solid (0.038 g, 45%): m.p. 190-191°C.

Analysis Calc. for $C_{20}H_{25}N_5O_2 \cdot 1/2\ H_2O$: C 63.81, H 6.96, N 18.60; found: C 64.07 H 6.79, N 18.54.

METHODS OF TREATMENT

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. The compounds of Formula (I) or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylatic or therapeutic treatment of any disease state in a human or other mammal which is mediated by inhibition of PDE IV, such as but not limited to asthma, allergic, or inflammatory diseases. The compounds of Formula (I) are administered in an amount sufficient to treat such a disease in a human or other mammal.

The method of treatment and monitoring for an HIV-infected human manifesting immune dysfunction or cytokine-mediated disease associated problems is taught in Hanna, WO 90/15534, December 27, 1990. In general, an initial treatment regimen can be copied from that known to be effective in interfering with TNF activity for other TNF mediated disease states by the compounds of Formula (I). Treated individuals will be regularly checked for T cell numbers and T4/T8 ratios and/or measures of viremia such as levels of reverse transcriptase or viral proteins, and/or for progression of monokine-mediated disease associated problems such as cachexia or muscle degeneration. If no effect is seen following the normal treatment regimen, then the amount of the monokine activity interfering agent administered is increased, e.g., by fifty percent per week.

The pharmaceutical composition of the present invention will comprise an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent. The compounds of Formula (I) are administered in conventional dosage forms prepared by combining a compound of Formula (I) in an amount sufficient to produce TNF production inhibiting activity, respectively, with standard pharmaceutical carriers according to conventional procedures. These procedures may involve mixing, granulating, and compressing or dissolving the ingredients as appropriate to the desired preparation.

Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1 gram. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates, or oils and are incorporated in a soft gelatin capsule shell. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine, or water with a flavoring or coloring agent.

The daily dosage regimen for oral administration is suitably about .001 mg/kg to 100mg/kg, preferably 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit activity.

While it is possible for an active ingredient to be administered neat, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of formulation, although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of Formulation.

Formulations of the present invention comprise an active ingredient together with one or more acceptable carrier(s) thereof and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of Formulation and not deleterious to the recipient thereof.

It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration, and other well-known variables.

No toxic effects are expected when these compounds are administered in accordance with the present invention.

UTILITY EXAMPLES

EXAMPLE A

Inhibitory effect of compounds of the Formula (I) on *in vitro* TNF production by human monocytes

The inhibitory effect of compounds of the Formula (I) on *in vitro* TNF production by human monocytes may be determined by the protocol as described in Badger *et al.*, EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

EXAMPLE B

Two models of endotoxic shock have been utilized to determine *in vivo* TNF activity for the compounds of the Formula (I). The protocol used in these models is described in Badger *et al.*, EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

The exemplified compounds herein demonstrated a positive *in vivo* response in reducing serum levels of TNF induced by the injection of endotoxin.

EXAMPLE C

Isolation of PDE Isozymes

The phosphodiesterase inhibitory activity and selectivity of the compounds of the Formula (I) can be determined using a battery of five distinct PDE isozymes. The tissues used as sources of the different isozymes are as follows: 1) PDE Ib, porcine aorta; 2) PDE Ic, guinea-pig heart; 3) PDE III, guinea-pig heart; 4) PDE IV, human monocyte; and 5) PDE V (also called "Ia"), canine tracheaolis. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic techniques [Torphy and Cieslinski, Mol. Pharmacol., 37:206-214, 1990]. PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography [Torphy *et al.*, J. Biol. Chem., 267:1798-1804, 1992].

Phosphodiesterase activity is assayed as described in the protocol of Torphy and Cieslinski, Mol. Pharmacol., 37:206-214, 1990. Positive IC_{50}'s in the nanomolar to μM range for compounds of the workings examples described herein for Formula (I) have been demonstrated.

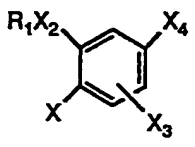
EXAMPLE D

The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. To assess the activity of PDE IV inhibition in intact cells, nondifferentiated U-937 cells (approximately 10^5 cells/reaction tube) were incubated with

various concentrations (0.01-1000 μM) of PDE inhibitors for one minute and 1μM prostaglandin E2 for an additional four minutes. Five minutes after initiating the reaction, cells were lysed by the addition of 17.5% perchloric acid, the pH was neutralized by the addition of 1M potassium carbonate and cAMP content was assessed by RIA. A general protocol for this assay is described in Brooker *et al.*, Radioimmunassay of cyclic AMP and cyclic GMP., Adv. Cyclic Nucleotide Res., 10:1-33, 1979. The compounds of the working examples as described herein for Formula (I) have demonstrated a positive EC_{50}s in the μM range in the above assay.

What is claimed is:

1. A compound of Formula (I):



(I)

wherein:

R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties may be optionally substituted with one or more halogens;

m is 0 to 2;

n is 1 to 4;

r is 1 to 6;

R_4 and R_5 are independently selected from hydrogen or a C_{1-2} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3} alkyl, halo substituted aryloxyC_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group;

provided that:

a) when R_6 is hydroxyl, then m is 2; or

b) when R_6 is hydroxyl, then r is 2 to 6; or

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

X is YR_2, halogen, nitro, NR_4R_5, or formyl amine;

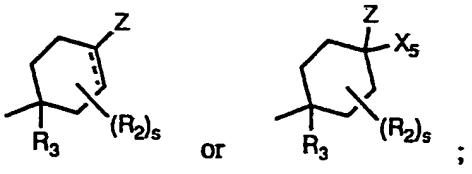
Y is O or $S(O)_{m'}$;

m' is 0, 1, or 2;

X_2 is O or NR_8;

X_3 is hydrogen or X;

X_4 is



(a) or (b);

X_5 is H, R_9, OR_8, CN, $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8R_8$, or NR_8R_8;

R_2 is independently selected from the group consisting of $-CH_3$ and $-CH_2CH_3$ optionally substituted by 1 or more halogens;

s is 0 to 4;

R_3 is hydrogen, halogen, C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, halo-substituted C_{1-4} alkyl, $-CH=CR_8'R_8'$, cyclopropyl optionally substituted by R_8', CN, OR_8, CH_2OR_8, NR_8R_{10}, $CH_2NR_8R_{10}$, $C(Z')H$, $C(O)OR_8$, $C(O)NR_8R_{10}$, or $C\equiv CR_8'$;

Z' is O, NR_9, NOR_8, NCN, $C(-CN)_2$, CR_8CN, CR_8NO_2, $CR_8C(O)OR_8$, $CR_8C(O)NR_8R_8$, $C(-CN)NO_2$, $C(-CN)C(O)OR_9$, or $C(-CN)C(O)NR_8R_8$;

Z is $C(Y')R_{14}$, $C(O)OR_{14}$, $C(Y')NR_{10}R_{14}$, $C(NR_{10})NR_{10}R_{14}$, CN, $C(NOR_8)R_{14}$, $C(O)NR_8NR_8C(O)R_8$, $C(O)NR_8NR_{10}R_{14}$, $C(NOR_{14})R_8$, $C(NR_8)NR_{10}R_{14}$, $C(NR_{14})NR_8R_8$ $C(NCN)NR_{10}R_{14}$, $C(NCN)SR_9$, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-, 4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-thiazolidinyl), or (2-, 4-, or 5-imidazolidinyl); wherein all of the heterocylic ring systems may be optionally substituted one or more times by R_{14};

the dotted line in formula (a) represents a single or double bond;

Y' is O or S;

R_7 is $-(CR_4R_5)_qR12$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three fluorines, -F, -Br, -Cl, $-NO_2$, $-NR_{10}R_{11}$, $-C(O)R_8$, $-C(O)OR_8$, $-OR_8$, -CN, $-C(O)NR_{10}R_{11}$, $-OC(O)NR_{10}R_{11}$, $-OC(O)R_8$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$, $-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_9$, $-S(O)_{m'}R_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

R_{12} is C_3-C_7-cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl;

R_8 is independently selected from hydrogen or R_9;

R_8' is R_8 or fluorine;

R_9 is C_{1-4} alkyl optionally substituted by one to three fluorines;

R_{10} is OR_8 or R_{11};

R_{11} is hydrogen, or C_{1-4} alkyl optionally substituted by one to three fluorines; or when R_{10} and R_{11} are as $NR_{10}R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O/N/or S;

R_{13} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{14} is hydrogen or R7; or when R_{10} and R_{14} are as $NR_{10}R_{14}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O, N, or S;

provided that:

f) when R_{12} is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1; or

g) when X_2R_1 is OCF_2H or OCF_3, X is F, OCF_2H or OCF_3, X_3 is H, s is zero, X_5 is H, Z is $C(O)OR_{14}$ and R_{14} is C_{1-7} unsubstituted alkyl, then R_3 is other than H;

or the pharmaceutically acceptable salts thereof.

2. A compound of claim 1 which is :

methyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylate;

4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylic acid;

methyl *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl *trans*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl *cis*- [4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate];

methyl *trans*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate], *tris*(hydroxymethyl)ammonium methane salt;

cis-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylate];

methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-cyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamide];

cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carboxamide];

trans-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carboxamide];

cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carbohydrazide];

cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-(2-acetylcarbohydrazide)];

cis-{4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(3-methyl[1,2,4]oxadiazol-5-yl)cyclohexane};

cis-{4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]oxadiazol-5-yl)cyclohexane};

cis-{4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]thiadiazol-5-yl)cyclohexane};

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-1-tris(methylthio)methylcyclohexane];

methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxamide];

methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxy-cyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1-carboxaldehyde];

methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylate];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid];

methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylate];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamic acid];

N-methyl-*cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamic acid];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-N-(2-cyanoethyl)carboxamide];

cis-[1-(2-cyanoethyl)-5-{4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl}tetrazole]; and

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-(tetrazol-5-yl)cyclohexane].

3. A pharmaceutical composition comprising a compound of Formula (I) according to claim 1 and a pharmaceutically acceptable excipient.

4. A method for treating an allergic or inflammatory state which method comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) according to claim 1 alone or in combination with a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

PCT/US93/01991

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/275; C07C 255/50
US CL :514/521,525; 558/426
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/521,525; 558/426 558/431; 548/31,136,252; 514/362,363,364,381

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Chemical Abstracts Structure Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 4,795,757 (Regan et al.) 03 January 1989 See example 1.	1-3
A	Chemical Abstracts, 12 March 1979, Agekyan et al. Abstract No. 90:86895p See formula I.	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 25 JUNE 1993	Date of mailing of the international search report 27 JUL 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer JACQUELINE HALEY Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01991

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I. Claims 1-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain a nitrogen-containing heterocyclic group, classified in Classes 544, 546 and 548, subclasses various.

II. Claims 1 and 3-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain none of group I compounds, supra and wherein the compounds contain a sulfur-containing heterocyclic group, classified in Class 549, subclasses 1-87.

III. Claims 1 and 3-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain none of groups 1-2 compounds, supra, and wherein the compounds contain an oxygen-containing heterocyclic group, classified in Class 549, subclasses 200+.

IV. Claims 1-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain none of groups 1-3 compounds, supra, and wherein the compounds contain a cyano group, classified in Class 558, subclasses 388-410.

V. Claims 1 and 3-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain none of groups 1-4 compounds, supra and wherein the compounds contain a C-CO-OR group, classified in Class 560, subclasses 8-113.

VI. Claims 1 and 3-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain none of groups 1-5 compounds, supra, and wherein the compounds contain a C-CO-OH group, classified in Class 562, subclasses 405-496.

VII. Claims 1 and 3-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain none of groups 1-6 compounds, supra, and wherein the compounds contain a N-CO-N group, classified in Class 564, subclass 32.

VIII. Claims 1 and 3-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain none of groups 1-7 compounds, supra, and wherein the compounds contain a N-CO-C group, classified in Class 564, subclass 123.

IX. Claims 1 and 3-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain none of groups 1-8 compounds, supra, and wherein the compounds contain a NH group, classified in Class 564, subclasses 225-299.

X. Claims 1 and 3-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain none of groups 1-9 compounds, supra, and wherein the compounds contain a NOH or NOR group, classified in Class 564, subclasses 300-443.

XI. Claims 1 and 3-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain none of groups 1-10 compounds, supra, and wherein the compounds contain a R-S-R group, classified in Class 568, subclass 38.

XII. Claims 1 and 3-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain none of groups 1-11 compounds, supra, and wherein the compounds contain a COH group, classified in Class 568, subclass 420.

XIII. Claims 1 and 3-4, drawn to compounds, compositions and methods of use wherein the compounds of formula I contain none of groups 1-12 compounds, supra, and wherein the compounds contain a R-O-R group, classified in Class 568, subclass 579.

The application lacks unity of invention under PCT Rules 13.1-13.4 since the claims herein vary in structure so much so as to fail to share a technical feature which defines a contribution over the prior art.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01991

Box I Observations where certain claims were found unsearchable (Continuation of item 1 f first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1,3-4 (each in part which corresponds to groups 4-6 as set forth above) and claim 2 (in its entirety).

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.